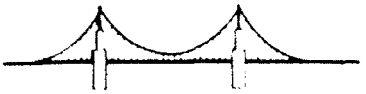

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A MATHEMATICAL MODEL FOR THE STUDY OF HEMORRHAGIC SHOCK AND FLUID RESUSCITATION: EXCHANGE OF FLUID AND SOLUTES BETWEEN VASCULAR, INTERSTITIAL, AND TISSUE CELL COMPARTMENTS

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Division of Military Trauma Research

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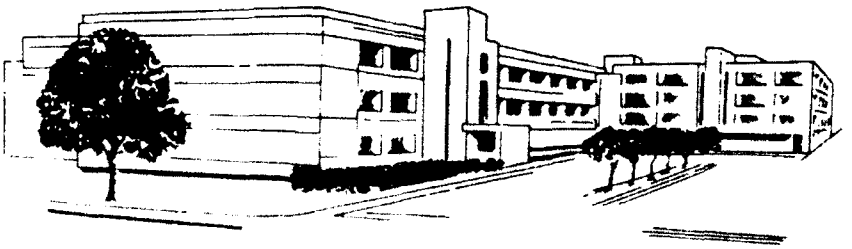

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The transfer of fluid from extravascular compartments into the vasculature is an important recovery mechanism for hemorrhage. This paper describes a three-compartment model (i.e., vascular, interstitial, and tissue cell) that predicts intra-extravascular fluid exchange following hemorrhage and fluid resuscitation. This three-compartment model assumes that capillary pressure is a linear function of blood volume, that interstitial pressure is a nonlinear function of extravascular volume, and that lymph flow is a function of interstitial pressure. Starting with this simple three-compartment model, the effects of model assumptions on plasma volume predictions were assessed. By varying model assumptions and comparing plasma volume predictions, we determined that separate tissue cell and interstitial compartments were required for predicting the plasma volume response to infusions of resuscitative solutions containing small, permeable solutes (e.g., NaCl). We also determined that the interstitial space could be described by a constant hydrostatic pressure, that considerations of interstitial exclusion volumes were not required, and that lymph flow could be considered constant. Plasma volume predictions generated by the three-compartment model were also compared to observed plasma volumes for validation. Data available for comparison included plasma volume responses to 1) rapid 33% loss of blood volume, 2) slow (60-minute) 50% loss of blood volume followed by 4 ml/kg administration of normal saline, 7.5% saline, 6% dextran-70, or 7.5% saline in 6% dextran-70, and 3) 4 ml/kg intravenous administration of 7.5% saline in 6% dextran-70 (no hemorrhage). Overall, model predictions compared well with observed plasma volumes. However, the model often responded more slowly than the observed biological system. In addition, secondary dynamics, when present in the biologic system, were frequently missing in the simulated system. Optimizing model parameter values, and incorporating cardiovascular dynamics and control, would be expected to remedy these problems.

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ABSTRACT

The transfer of fluid from extravascular compartments into the vasculature is an important recovery mechanism for hemorrhage. This paper describes a three-compartment model (i.e., vascular, interstitial, and tissue cell) that predicts intra-extravascular fluid exchange following hemorrhage and fluid resuscitation. This three-compartment model assumes that capillary pressure is a linear function of blood volume, that interstitial pressure is a nonlinear function of extravascular volume, and that lymph flow is a function of interstitial pressure. Starting with this simple three-compartment model, the effects of model assumptions on plasma volume predictions were assessed. By varying model assumptions and comparing plasma volume predictions, we determined that separate tissue cell and interstitial compartments were required for predicting the plasma volume response to infusions of resuscitative solutions containing small, permeable solutes (e.g., NaCl). We also determined that the interstitial space could be described by a constant hydrostatic pressure, that considerations of interstitial exclusion volumes were not required, and that lymph flow could be considered constant. Plasma volume predictions generated by the three-compartment model were also compared to observed plasma volumes for validation. Data available for comparison included plasma volume responses to 1) rapid 33% loss of blood volume, 2) slow (60-minute) 50% loss of blood volume followed by 4 ml/kg administration of normal saline, 7.5% saline, 6% dextran-70, or 7.5% saline in 6% dextran-70, and 3) 4 ml/kg intravenous administration of 7.5% saline in 6% dextran-70 (no hemorrhage). Overall, model predictions compared well with observed plasma volumes. However, the model often responded more slowly than the observed biological system. In addition, secondary dynamics, when present in the biologic system, were frequently missing in the simulated system. Optimizing model parameter values, and incorporating cardiovascular dynamics and control, would be expected to remedy these problems.

key words: model, hemorrhage, fluid resuscitation, transcapillary exchange, body fluid shifts.

A Mathematical Model for the Study of Hemorrhagic Shock and Fluid Resuscitation: Fluid and Solute Exchange Between Vascular, Interstitial, and Tissue Cell Compartments -- Tammy J. Doherty

INTRODUCTION

Following a loss of blood volume, capillary hydrostatic pressure is reduced and fluid is transferred from extravascular compartments into the vasculature. An increase in blood volume has the opposite effect, a net transfer of fluid out of the vasculature into the interstitium. Net fluid influx or efflux may also occur when plasma osmolarity is altered as a result of plasma volume changes or administration of resuscitative fluids. These results may be predicted, qualitatively, using the Landis-Starling Equation[1,2], which relates the rate of vascular fluid efflux (J_v) to hydrostatic (P) and osmotic (Π) pressure differences across the capillary wall:

$$J_v = k_v[(P_C - P_I) - (\Pi_C - \Pi_I)] \quad (1)$$

where capillary pressures are designated by the subscript C, and interstitial pressures by the subscript I.

Although the Landis-Starling Equation provides a good approximation for transcapillary fluid shifts that occur at steady state or over a short period, this equation does not account for capillary wall permeability to solutes, which plays an important role in the plasma volume response to changes in blood volume and plasma osmolality. In a previous paper[3] we reviewed and compared various models of transcapillary fluid and solute flux and found that the Kedem-Katchalsky equations[4] could be used to describe the efflux of fluid (J_v) and solute (J_s) from the capillary to the interstitial space in response to changes in blood volume and plasma osmolarity:

$$J_v = k_v\left[(P_C - P_I) - \sum \sigma_s(\Pi_{s,C} - \Pi_{s,I})\right] \quad (2)$$

$$J_s = k_s(C_{s,C} - C_{s,I}) - (1 - \sigma_s)\bar{C}_s J_v \quad (3)$$

where σ_s is the reflection coefficient for solute s at the capillary wall, $C_{s,C}$ and $C_{s,I}$ are capillary and interstitial concentrations of solute s, and $\bar{C}$ is the average solute concentration for capillary and interstitial fluid. The present paper explores other aspects of modeling intra-to-extravascular exchange. Starting with a simple three-compartment (i.e., blood, interstitial, and tissue cell) model, the effects of model assumptions on plasma volume predictions are assessed. Specifically, the effects of interstitial-to-tissue cell fluid exchange, interstitial compliance, interstitial macromolecular exclusion volumes, and lymph flow are examined. Finally, plasma volume predictions, generated by the three-

compartment model, are compared to experimentally observed plasma volumes for validation.

THE BASIC 3-COMPARTMENT MODEL

The three-compartment model, initially selected to describe intra-to-extravascular fluid and solute transport, is shown schematically in Figure 1. Rates of compartment volume change (dV/dt) for plasma (subscript P), interstitial (subscript I) and tissue cell (subscript T) compartments may be obtained by subtracting appropriate rates of fluid efflux from rates of fluid influx:

$$\frac{dV_P}{dt} = F_v - H_v + L_v - J_{v,PI} \tag{4}$$

$$\frac{dV_I}{dt} = J_{v,PI} - L_v - J_{v,IT} \tag{5}$$

$$\frac{dV_T}{dt} = J_{v,IT} \tag{6}$$

where F_v is the rate of resuscitative fluid administration, H_v is the rate of plasma volume loss in hemorrhaged blood, L_v is the rate of lymph return, and $J_{v,ij}$ is the rate of fluid efflux from compartment i to compartment j. Similarly, changes in plasma solute mass (dS/dt) for the three compartments may be obtained by subtracting solute efflux from influx rates:

$$\frac{dS_P}{dt} = F_s - H_s + L_s - J_{s,PI} \tag{7}$$

$$\frac{dS_I}{dt} = J_{s,PI} - L_s \tag{8}$$

where F_s is the rate of solute administration via resuscitative fluid, H_s is the rate of solute loss in hemorrhaged blood, L_s is the rate of solute return to the vasculature via the lymphatics, and $J_{s,PI}$ is the rate of solute efflux from the vasculature to the interstitium. Solute transport between interstitial and tissue cell compartments is assumed to be zero.

The Kedem-Katchalsky[4] equations (Equations 2 and 3) are used to describe the coupled flux of fluid ($J_{v,Pl}$) and solute ($J_{s,Pl}$) across the capillary wall:

$$J_{v,Pl} = k_{v,Pl}\left[(P_C - P_I) - \sum \sigma_{s,Pl}(\Pi_{s,P} - \Pi_{s,I})\right] \quad (9)$$

$$J_{s,Pl} = k_{s,Pl}(C_{s,P} - C_{s,I}) + (1 - \sigma_{s,Pl})\bar{C}_{s,Pl} J_{v,Pl} \quad (10)$$

Because the tissue cell wall is considered to be impermeable to solutes, the Landis-Starling equation (Equation 1), extended to a solution of multiple solutes, may be used to describe fluid transport from the interstitial to the tissue cell compartment:

$$J_{v,IT} = k_{v,IT}\left[(P_I - P_T) - \sum (\Pi_{s,I} - \Pi_{s,T})\right] \quad (11)$$

A model for lymph flow (L_v) as a function of interstitial hydrostatic pressure was obtained from the fluid and solute transport model developed by Mazzoni and coworkers[5]:

$$L_v = \begin{cases} 0 & when\ P_I \le -6\,mm\,Hg \\ 0.02 + 0.00333 P_I & when\ -6 \le P_I < 0 \\ 0.02 + 0.105 P_I & when\ 0 \le P_I < 4 \\ 0.44 & when\ 4 \le P_I \end{cases} \quad (12)$$

Transport of solutes in lymph is assumed to occur by bulk flow, i.e.:

$$L_s = C_{s,I} L_v \quad (13)$$

To obtain estimates for capillary pressure (P_C), it is assumed that a rapid change in blood volume results in a 3 mm Hg change in arterial pressure for each 1 ml/kg change in blood volume[6], and that changes in capillary pressure are proportional to changes in arterial pressure by a factor of approximately 0.17[7]. These assumptions yield the following relationship between capillary pressure and blood volume (V_B):

$$P_C = 0.51(V_B - V_{B_0}) + P_{C_0} \quad (14)$$

where V_{Bo} and P_{Co} are initial values. Interstitial hydrostatic pressure is estimated using a piece-wise linear relationship between P_I and V_I, adapted from the transport model developed by Mazzoni et al.[5]:

$$P_I = \begin{cases} 1.042(V_I + V_T - 490) & when\ V_I + V_T < 490 \\ 0.00323(V_I + V_T - 490) & when\ 490 < V_I + V_T < 833 \\ 1.106 & when\ 833 < V_I + V_T \end{cases} \quad (15)$$

For simplicity, three plasma solutes were considered: salts (subscript s), albumin (subscript a), and globulins (subscript g). Dextrans of approximately 70 kD (subscript d), present in some artificial plasma volume expanders, were also considered. Because NaCl is the most abundant salt in plasma and interstitial fluid, the characteristics of NaCl were selected to represent all salt molecules. The osmotic pressure for NaCl is approximately[8]:

$$\Pi_s = (31.877)(19.33\times10^3)C_s \quad (16)$$

where C_s is salt concentration (g/ml), 31.877 converts grams of NaCl to milliosmoles, and 19.33×10^3 is the osmotic pressure (mm Hg) exerted by 1 mosm/ml of solute at normal body temperature. Cubic equations, presented by Landis and Pappenheimer[9], are used to estimate partial osmotic pressures for albumin and globulin:

$$\Pi_a = 280C_a + 1800C_a^2 + 12000C_a^3 \quad (17)$$

$$\Pi_g = 210(C_a + C_g) + 1600(C_a + C_g)^2 + 9000(C_a + C_g)^3 - \Pi_a \quad (18)$$

where C_a and C_g are concentrations (g/ml) of albumin and globulin, respectively. Partial osmotic pressures of dextran-70 were estimated from the cubic relationship developed by Mazzoni et al.[5] from experimental data provided by Thorén[10]:

$$\Pi_d = 620C_d + 9300C_d^2 + 5000C_d^3 \quad (19)$$

where C_d is dextran-70 concentration (g/ml).

TISSUE CELL AND INTERSTITIAL COMPARTMENTS

In the basic three-compartment model described above, both tissue cell and interstitial compartments are considered. However, tissue cells cannot support a hydrostatic pressure gradient and osmotic pressure gradients across the cell membrane are usually negligible. Thus, it may be possible to lump the tissue cell and interstitial compartments together into a single extravascular compartment. On the other hand, the capillary wall is much more permeable to certain solutes (e.g., sodium) than are tissue cell membranes. Consequently, intravascular administration of permeable hyperosmotic solutions, and subsequent transport of the solutes to the interstitial space could produce large osmotic gradients across the cell wall. Such gradients could alter the amount of fluid translocated from the extravascular to the vascular space, in which case separate tissue cell and interstitial compartments would be warranted.

To test whether two extravascular compartments are required, we generated a two-compartment model by eliminating the interstitial-cellular fluid transport equation (Equation 11) from the three-compartment model. As Figure 2 shows, predictions of plasma volume response to an instantaneous 25% increase or decrease in blood volume, or an instantaneous 50% increase or decrease in plasma albumin were indistinguishable for the two-compartment and basic three-compartment models (prediction curves overlap). However, predictions of plasma volume response to gross changes in plasma NaCl differed.

Because of high osmotic pressure gradients across the capillary wall, both the two- and three-compartment models initially predict a high influx of fluid from the interstitium to the vasculature (Figures 3a and 4a) . Due to the high capillary permeability to NaCl, there is also an immediate increase in interstitial NaCl concentration (Figures 3b and 4b). In the three- compartment model, this change in interstitial NaCl concentration results in a transfer of fluid from the tissue cells to the interstitial space. Fluid moves from the tissue cell to interstitium, and from there to the vasculature, until the net driving force for fluid flow across the capillary wall favors net vascular fluid efflux. Eventually, plasma and interstitial volumes return to normal levels. In the two-compartment model, there is no tissue cell fluid reservoir for interstitial NaCl dilution. Thus, plasma and interstitial NaCl concentrations equilibrate more rapidly, and the driving force for fluid transfer across the capillary wall favors net vascular fluid efflux sooner. Although the steady-state result (i.e., normal plasma volume) is the same for the two models, the short-term effects of NaCl infusion are different; the two-compartment model predicts a smaller peak plasma volume response, and an earlier return of plasma volume to normal levels. Because the increase in plasma volume associated with hyperosmotic

resuscitative fluid administration may be exploited therapeutically, we feel that for accuracy, separate tissue and interstitial compartments must be included in the model.

CHARACTERISTICS OF THE INTERSTITIAL COMPARTMENT

The interstitial matrix is made up of a network of hyaluronic acid molecules, proteoglycans, and cross-linked collagen fibers[11]. The mechanical-elastic properties of the collagen molecules contribute to the development of nonlinear interstitial pressure-volume relationships which differ from pressure-volume relationships of fluid-filled compartments. When the interstitium is dehydrated, the pressure-volume relationship is dominated by the mechanical elastic properties of the collagen fibers. At normal interstitial volumes, the contribution of mechanical forces declines. At higher interstitial volumes, the gelatin matrix begins to break up (collagen fibers do not tolerate expansion well) and the pressure-volume relationship assumes the characteristics of a fluid-filled compartment, dominated by the elastic effects of the outer boundaries of the extravascular space[12]. The set of equations used to estimate interstitial hydrostatic pressure (Equation 15) corresponds to this description, consisting of a relatively steep pressure-volume relationship at below-normal volumes and a more compliant region at above-normal volumes[13].

To test whether such detailed characterization of the extravascular pressure-volume relationship is required for accurate predictions of plasma volume, we compared plasma volume predictions generated by the basic three-compartment model (in which the piece-wise linear interstitial pressure-volume relationship of Equation 15 is used) with plasma volume predictions generated by a model in which interstitial pressure is fixed at 0 mm Hg. The results of the simulations are presented in Figure 5. The two models produce nearly identical predictions (i.e., prediction curves overlap) for each of the simulated changes in blood volume and plasma solute concentration. These results suggest that the nonlinearity of interstitial compliance is unimportant in predictions of whole-body plasma volume changes following hemorrhage and/or fluid resuscitation.

The hyaluronic acid molecules, proteoglycans, and cross-linked collagen fibers of the interstitial gel occupy a significant volume of the interstitial space. The effect of these molecules on surrounding fluid is to restrict the total interstitial fluid volume available to macromolecules. Interstitial exclusion volumes for albumin are usually measured in the range of 40-50%[11] which might affect interstitial solute concentration changes. To test the effect of

macromolecular exclusion volumes on intra-to-extravascular fluid and solute exchange, plasma volumes generated by the basic three-compartment model were compared to predictions generated by a model in which only 50% of the interstitial compartment is available for the diffusion of macromolecules. As Figure 6 demonstrates, there was no apparent difference in plasma volume predictions generated by the two models. Thus, exclusion volumes may be neglected in studies of plasma volume response to changes in blood volume and plasma osmolarity.

TRANSPORT OF SOLUTE AND SOLVENT IN LYMPH

Under normal circumstances, Starling forces favor net fluid efflux at the arteriolar end of the capillary and net fluid absorption at the venular end. Net fluid efflux which is not returned to the circulation via transcapillary flux is normally returned by the lymphatics. Lymph vessels originate as thin-walled, capillary-like, close-ended channels and are present in all tissues. At the origin, sequential endothelial cells overlap each other with fine collagen fibrils anchoring the non-overlapping portions to large collagen bundles and ground substance in surrounding tissues[13]. Because the anchoring filaments are not attached to the overlapping portions, distension of the interstitial matrix causes the endothelial cells to be pulled apart, lowering lymphatic pressure. A positive interstitial-lymph pressure gradient causes the overlapping portion of the endothelial cells (i.e., the "flaps") to be pushed inward, admitting flow into the lymphatic capillary while prohibiting back flow. Further from the origin, lymphatic endothelial cells are closer together, forming a true vessel capable of transporting both fluid and solute. Small lymph capillary vessels join together to form progressively larger lymph vessels. Lymph flow is achieved by rhythmic contraction of smooth muscle cells in large lymph vessels, which tends to push flow from origin to circulation while valves present in prenatal lymph vessels prohibit back-flow[12]. The level of smooth muscle activity may be under sympathetic control[14]. From this conceptual model, we may presume that the rate of fluid transfer from the interstitium into the lymphatics, and from there to the vasculature depends on interstitial pressure, interstitial volume, and lymphatic smooth muscle activity.

In the basic three-compartment model, lymph flow rates were assumed to be dependent upon interstitial hydrostatic pressures (Equation 12). Figure 7 shows that a model that assumes constant lymph flow rates (i.e., 0.02 $ml \cdot kg^{-1} \cdot g \cdot min^{-1}$) generates the same plasma volume predictions as the basic three-compartment model for the simulated conditions included for testing (prediction curves overlap). Pathological conditions normally associated with tissue edema,

such as increased capillary permeability to macromolecules, were not included in this study.

MODEL VALIDATION

Results of the previous sections indicate the possibility of simplifying the basic three-compartment model by ignoring interstitial hydrostatic pressure changes, interstitial macromolecular exclusion volumes, and lymph flow rate changes. In this section, we attempt to determine whether the basic three-compartment model is adequate for predicting the plasma volume response to changes in blood volume and plasma osmolarity. Data available for comparison include plasma volume responses to 1) rapid uncontrolled hemorrhage, 2) slow fixed-volume hemorrhage followed by small-volume resuscitation, and 3) hyperosmotic resuscitative fluid administration (no hemorrhage). Model parameter values and initial values used in this comparison study are provided in Tables 1 and 2. These values were obtained from the literature and were not optimized for this study.

In the first validation experiment, predicted plasma volumes were compared to experimental data from an uncontrolled, aortotomy hemorrhage model in splenectomized swine[15]. In this aortotomy model, a 5 mm longitudinal slit is made in the abdominal aorta. Blood loss is rapid, but abates after 2-5 minutes by normal hemostatic mechanisms. The total blood loss is between 31% and 35% of the normal blood volume for this species. Percent changes in plasma volume were computed by assuming that percent increases in plasma volume equaled percent decreases in systemic hematocrit. These calculated plasma volume changes are plotted using dotted lines in Figure 8. Predicted plasma volumes (solid line in Figure 8) approximated the response of the anesthetized animals. However, the model was unable to follow the dynamic changes in plasma volume that occurred during the recovery period. This lack of agreement may be the result of changes in cardiovascular hemodynamics and cardiovascular control which are not accounted for in the model. Cardiovascular control mechanisms affect the overall plasma volume, a fact that is supported by the apparent differences between plasma volume responses of anesthetized and conscious animals in this study. Disparities between observed and predicted plasma volumes may also be due to red blood cell trapping or red blood cell skimming in the microvasculature[16], factors which affect systemic hematocrits and calculated plasma volumes. Finally, the lack of secondary dynamics in the predicted plasma volume response could be the result of inappropriate parameter value selection.

In the second set of validation experiments, we compared predicted plasma volumes with the observed plasma volume response to a 50% fixed-volume hemorrhage in conscious, splenectomized swine[17]. In this hemorrhage model, 7.5 ml/kg of blood was withdrawn over successive intervals beginning at 0, 9, 19, 31.5, and 44 minutes. The total hemorrhage volume of 37.5 ml/kg was approximately 50% of the animal's initial blood volume. Observed plasma volume changes were computed from percent changes in systemic hematocrit. Plasma volume predictions overestimated observed responses by a relatively large margin (Figure 9). Better predictions were achieved by adjusting the capillary filtration coefficient (k_{cpl}) downward by 50% (Figure 9 dashed line).

At the end of the hemorrhage (60 minutes), the animals were resuscitated with 4 ml/kg of normal saline (NS), hypertonic 7.5% saline (HS), hyperosmotic 6% dextran-70 (HD), or hypertonic 7.5% saline in 6% dextran (HSD). As Figure 10 shows, when the capillary filtration coefficient was adjusted by -50%, model predictions agreed with the response of plasma volume to resuscitation with HS and HSD. The model was less successful in predicting the response to HD, and was unsuccessful at predicting the response to normal saline (NS). The reason for the lack of agreement between model predictions and observed plasma volume response to normal saline infusion is most likely the physiologic state of the animals in the NS group. Only 2 of 6 animals survived the first 15 minutes after resuscitation, and all died after 60 minutes. Survival was low in the HD group as well, with a gradual attrition in subject numbers to 33% (2 of 6) at 60-minutes post-hemorrhage and 16.5% (1 of 6) at 120-minutes. As in previous attempts to predict the plasma volume response to aortotomy hemorrhage, the model appeared to miss some of the secondary dynamics of the plasma volume response to hyperosmotic solutions. Again, this could be due to a number of factors including the lack of cardiovascular hemodynamics, the lack of cardiovascular control mechanisms, and the need to refine model parameter values.

In the final set of validations, model predictions were compared to plasma volume responses of anesthetized, euvolemic swine to infusion of 4 ml/kg of HSD[18]. As Figure 11 shows, predicted plasma volumes agreed with the observed plasma volume response. However, the model responded more slowly than the observed system. In addition, secondary dynamics (apparent between 5 and 20 minutes after infusion) were lacking. Perhaps these discrepancies, as in the previous validations, may be explained or reduced by considerations of cardiovascular hemodynamics and control, and by optimization of model parameter values.

SUMMARY AND CONCLUSIONS

In this paper, we present a simple three-compartment model to describe transvascular fluid exchange following hemorrhage and fluid resuscitation. This model includes equations for fluid and solute transport across the capillary wall, between interstitium and tissue cell, and in lymph. By varying model assumptions and comparing resulting plasma volume predictions, we determined that separate tissue cell and interstitial compartments were required for predicting the plasma volume response to infusions of resuscitative solutions containing small, permeable solutes (e.g., NaCl). We also determined that the interstitial space could be described by a constant hydrostatic pressure, that considerations of interstitial exclusion volumes were not required, and that lymph flow could be considered constant.

The model described in this paper can, with little or no adjustment of model parameter values, predict the general response of plasma volume to simulated hemorrhage insults and simulated infusions of isosmotic and hyperosmotic solutions. However, the model often responds more slowly than the observed biological systems, and secondary dynamics evident in the observed biological systems are frequently lacking. The most apparent weakness in this model is its description of the vasculature as an elastic compartment, represented by a linear relationship between capillary pressure and blood volume. This description was chosen to facilitate model comparisons and is not presumed to be accurate. By combining the flux model described here with a model of cardiovascular hemodynamics, and by optimizing parameter values, prediction accuracy is expected to improve.

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Table 1. Initial conditions and parameter values for the three-compartment model.

<u>blood compartment</u>	
Blood Volume (V_B)	70 ml/kg
Plasma Volume (V_P)	38.5 ml/kg
Plasma NaCl Concentration ($C_{s,P}$)	0.0093 g/ml
Plasma Albumin Concentration ($C_{a,P}$)	0.045 g/ml
Plasma Globulin Concentration ($C_{g,P}$)	0.025 g/ml
Capillary Hydrostatic Pressure (P_C)	18.5 mm Hg
<u>interstitial compartment</u>	
Interstitial Volume (V_I)	140 ml/kg
Interstitial NaCl Concentration ($C_{s,I}$)	0.0093 g/ml
Interstitial Albumin Concentration ($C_{a,I}$)	0.02 g/ml
Interstitial Globulin Concentration ($C_{g,I}$)	0.0 g/ml
Interstitial Hydrostatic Pressure (P_I)	0.0 mm Hg
<u>tissue-cell compartment</u>	
Tissue Volume (V_T)	350 ml/kg

Table 2. Parameter values for fluid and solute transport equations.

assumed values	
σ_s	0.109
σ_a	0.904
σ_g	1.0
k_s	35.71 $ml \cdot kg^{-1} \cdot min^{-1}$
k_a	0.013504 $ml \cdot kg^{-1} \cdot min^{-1}$
$k_{v,PI}$	0.0612 $ml \cdot kg^{-1} \cdot min^{-1} \cdot mm\ Hg^{-1}$
$k_{v,IT}$	0.45501 $ml \cdot kg^{-1} \cdot min^{-1} \cdot mm\ Hg^{-1}$

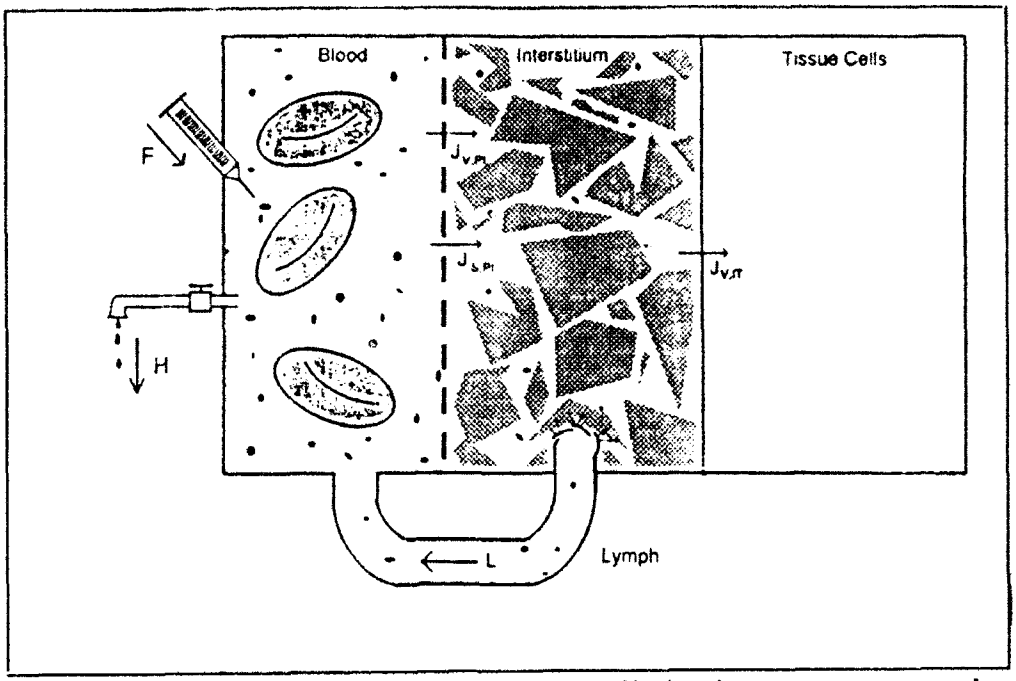

Figure 1. Three-compartment model for predicting intra-to-extravascular fluid and solute exchange.

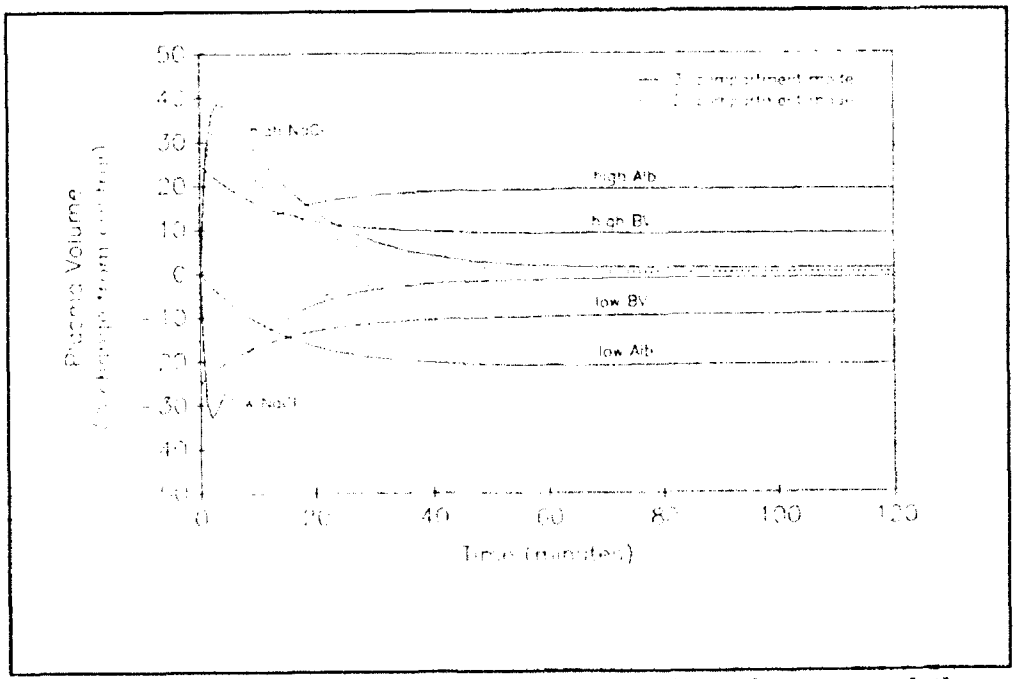

Figure 2. Plasma volume predictions generated by the two- and three-compartment models.

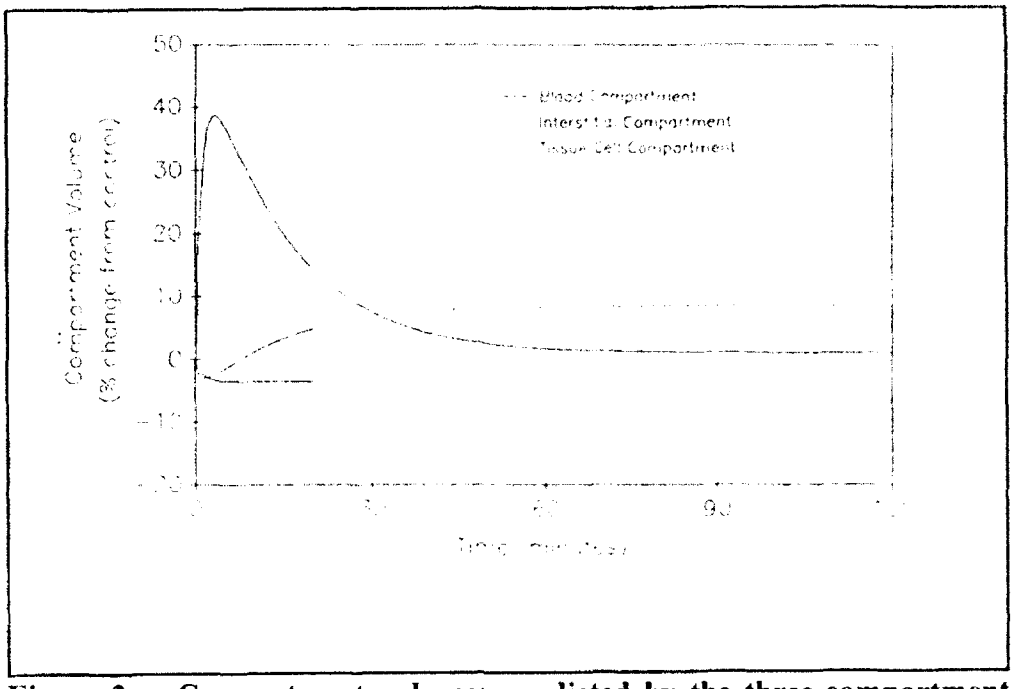

Figure 3a. Compartment volumes predicted by the three-compartment model following a simulated 50% increase in plasma NaCl concentration.

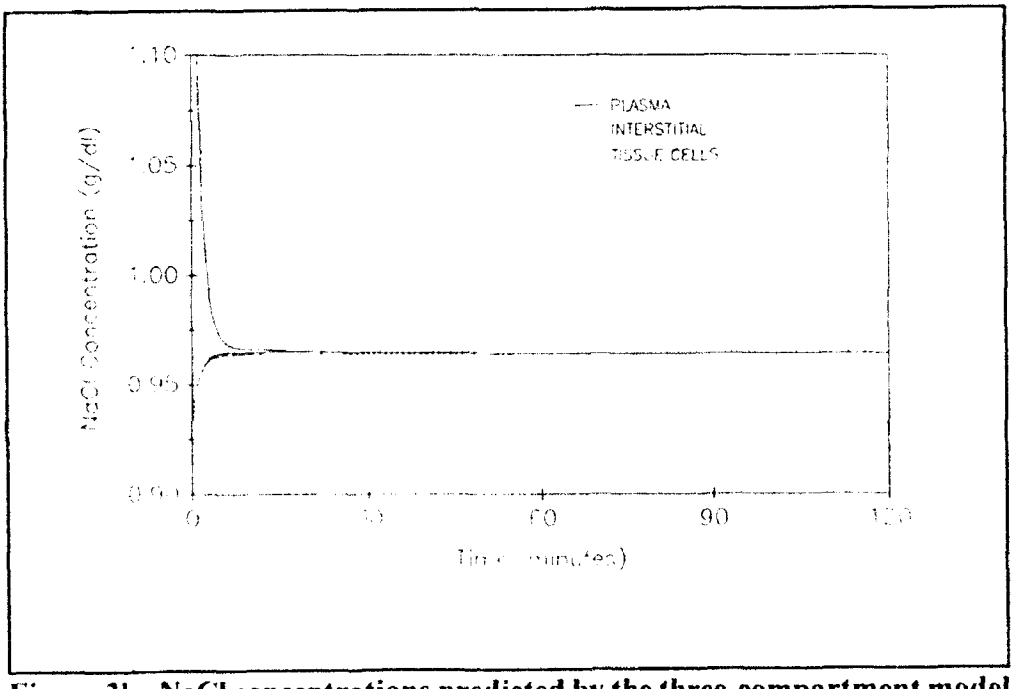

Figure 3b. NaCl concentrations predicted by the three-compartment model following a simulated 50% increase in plasma NaCl concentration.

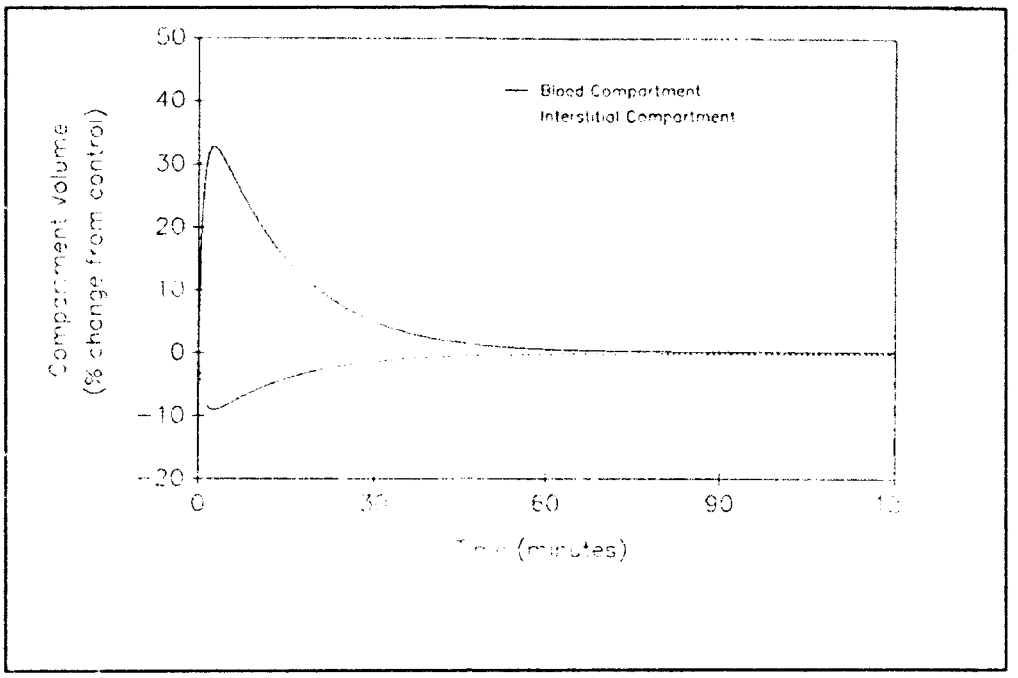

Figure 4a. Compartment volumes predicted by the two-compartment model following a simulated 50% increase in plasma NaCl concentration.

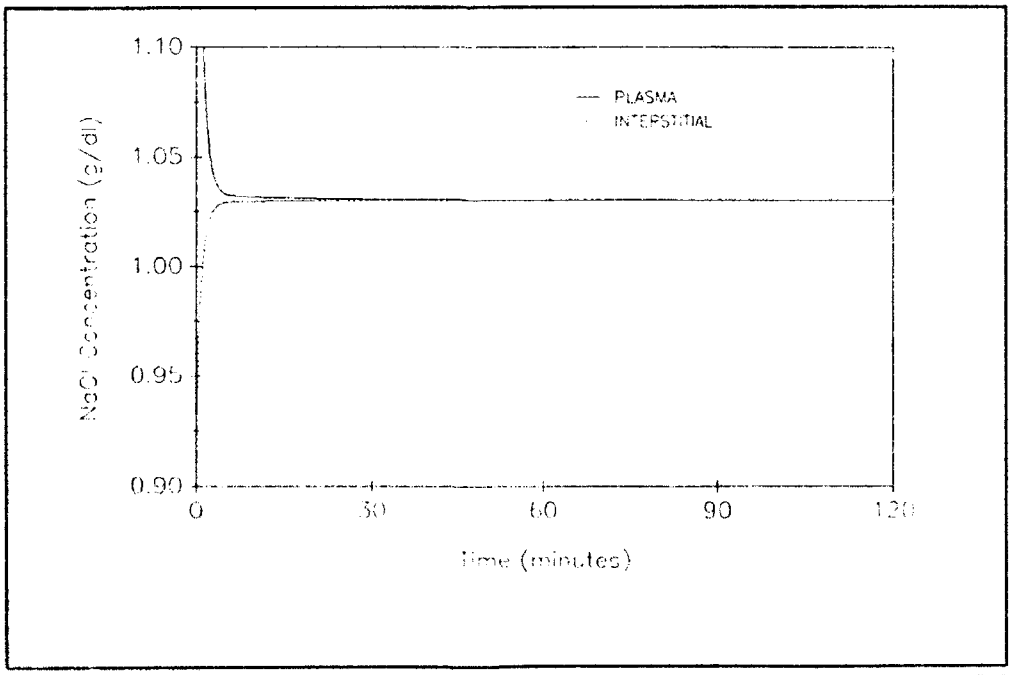

Figure 4b. NaCl concentrations predicted by the two-compartment model following a simulated 50% increase in plasma NaCl concentration.

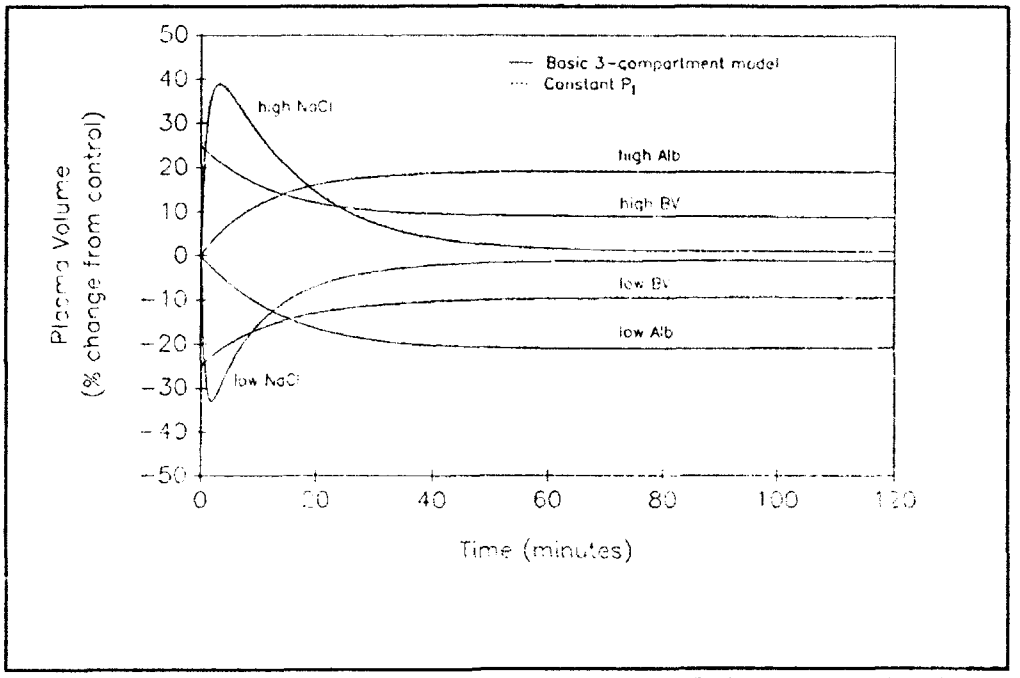

Figure 5. Plasma volume predictions generated by the basic three-compartment model and predictions generated by a model assuming a constant interstitial hydrostatic pressure.

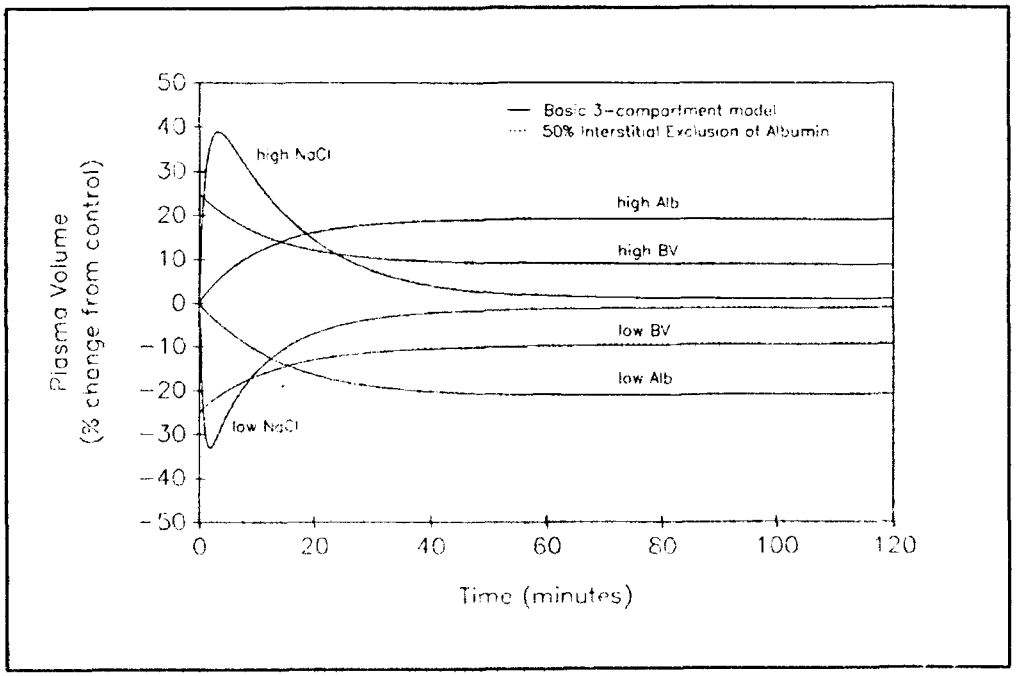

Figure 6. Plasma volume predictions generated by the three-compartment model and predictions generated by a model assuming a 50% exclusion volume for albumin.

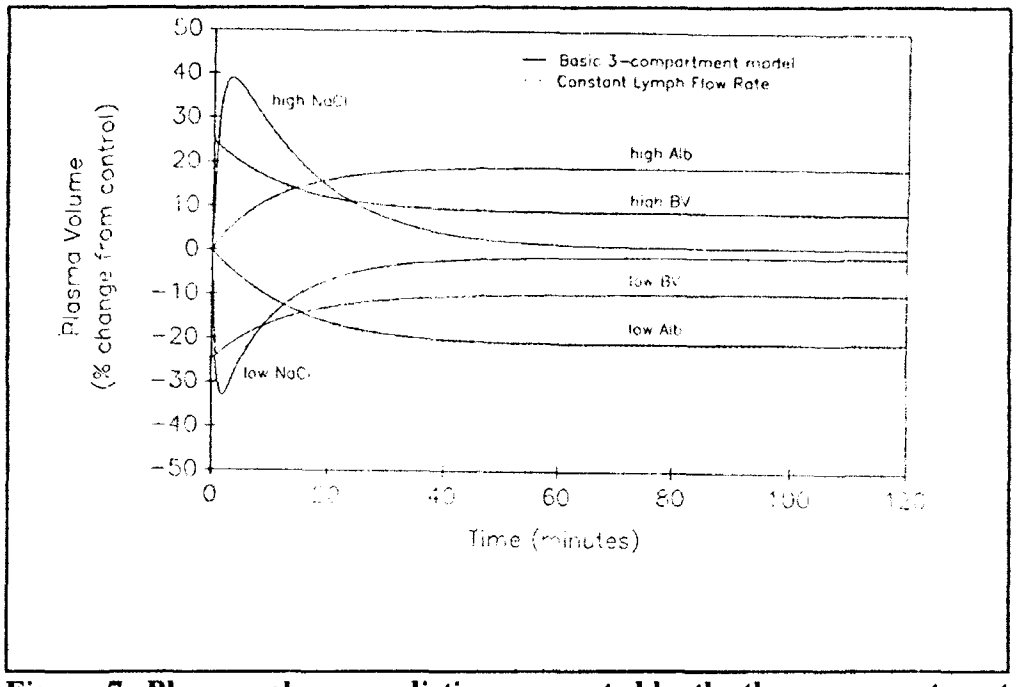

Figure 7. Plasma volume predictions generated by the three-compartment model and by a model assuming constant lymph flow rates.

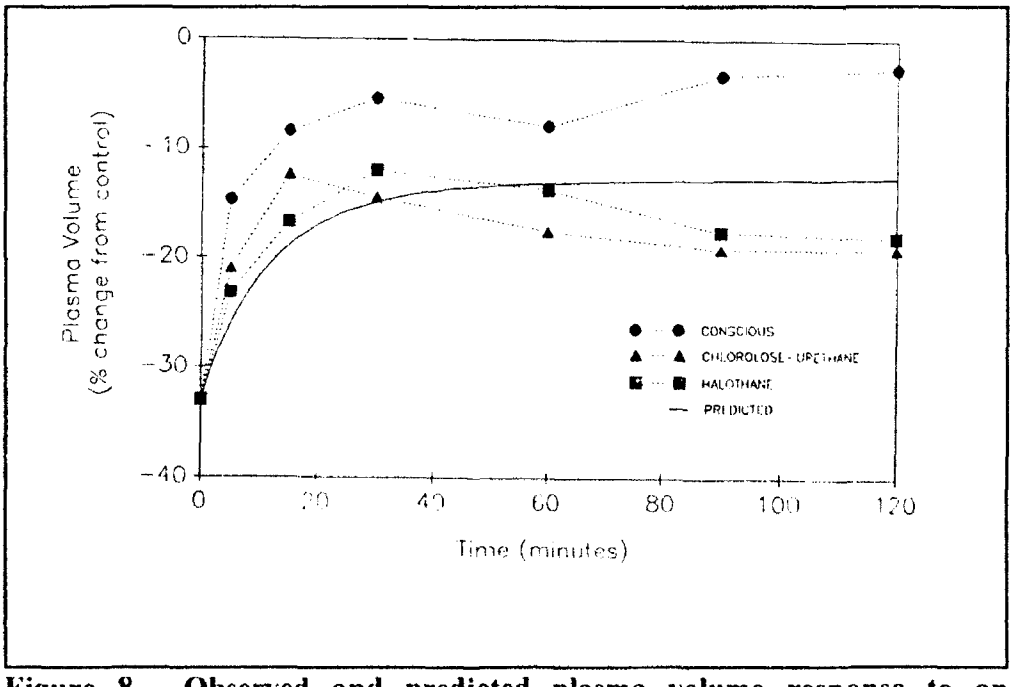

Figure 8. Observed and predicted plasma volume response to an instantaneous 33% loss of blood volume.

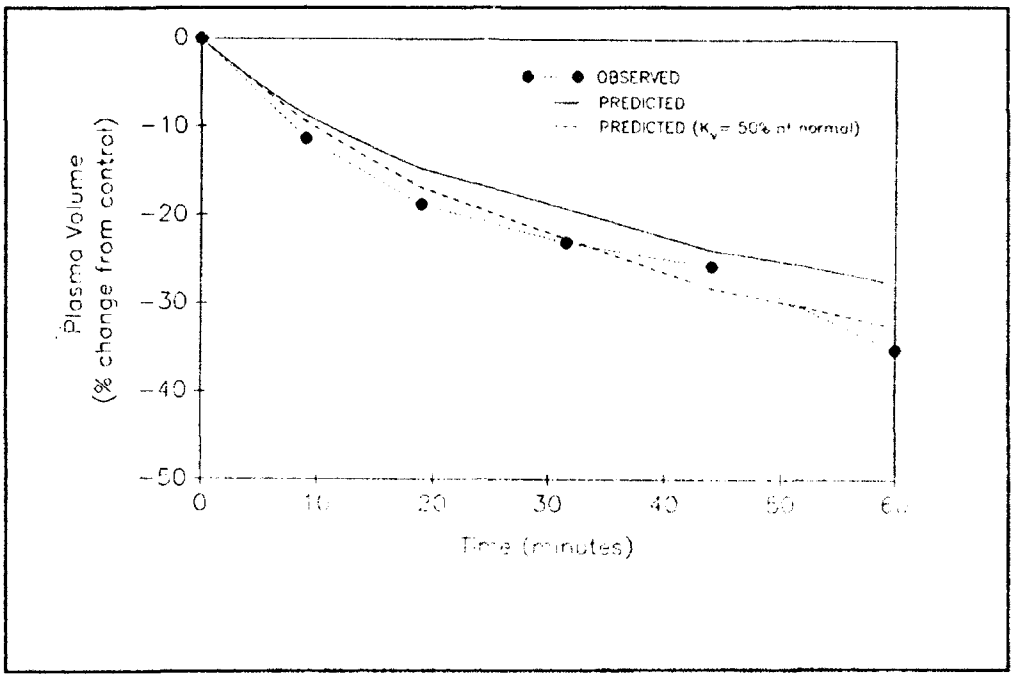

Figure 9. Observed and predicted plasma volume response to an exponential 50% loss of blood volume.

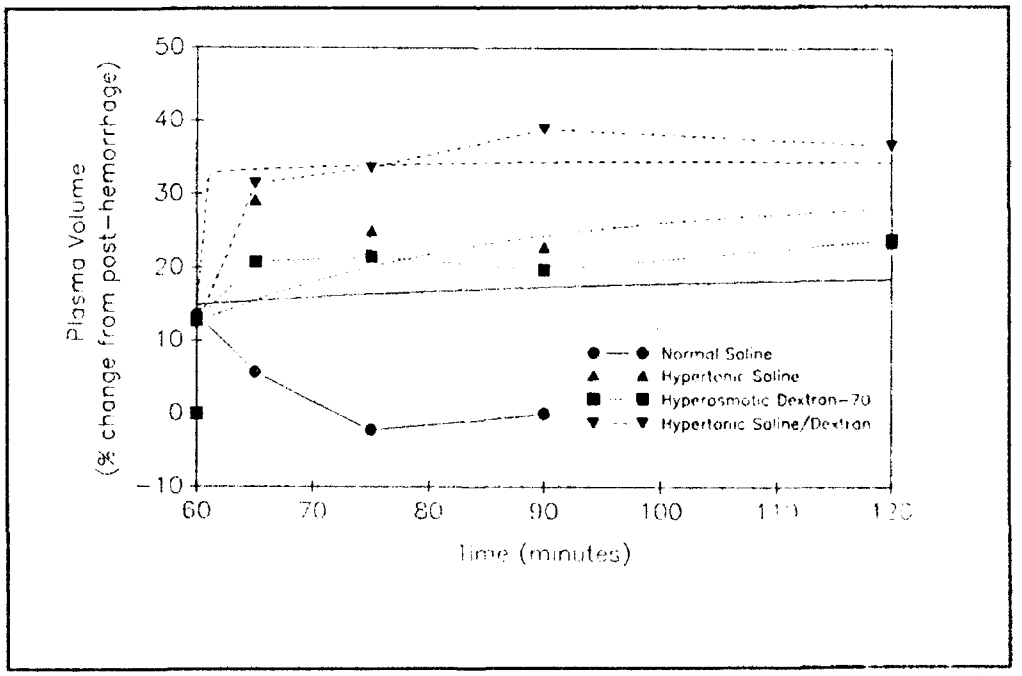

Figure 10. Observed and predicted plasma volume response to 4 ml/kg resuscitation following a 50% exponential hemorrhage.

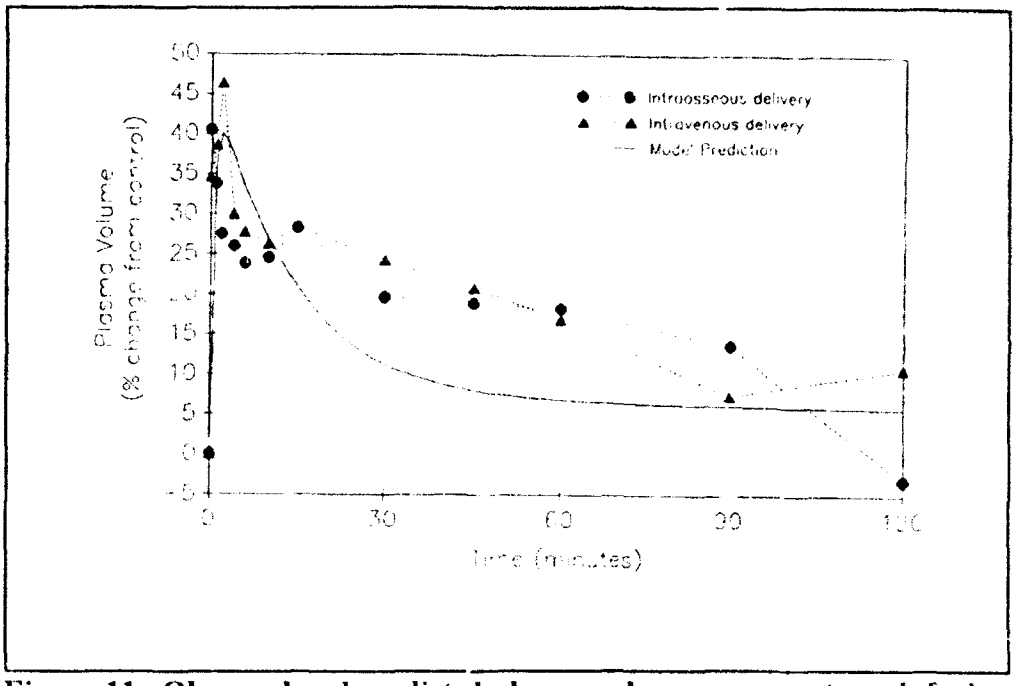

Figure 11. Observed and predicted plasma volume response to an infusion (4 ml/kg) of 7.5% NaCl in 6% dextran-70 (no hemorrhage).

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